Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and Later-Onset Fabry disease

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Abstract: Background: Fabry disease (FD), an X-linked lysosomal storage disorder, results from the deficient activity of -galactosidase A (-Gal A) and the accumulation of its substrates, globotriaosylceramide (Gb3) and its deacylated derivative, globotriaosyl-sphingosine (Lyso-Gb3). Here, we compared the levels of Lyso-Gb3 in dried blood spots (DBS) and sera in affected males and heterozygotes with the "Classic" and "Later-Onset" phenotypes. Methods: The Lyso-Gb3 concentrations in DBS and sera from 56 FD patients were determined by highly sensitive electrospray ionization liquid chromatography tandem mass spectrometry. Results: The serum Lyso-Gb3 levels in 18 and 5 affected males with the Classic and Later-Onset phenotypes, were 61 ± 38 and 14 ± 12 ng/mL, respectively. Lyso-Gb3 levels in 30 females from Classic families and three females from Later-Onset families were 10 ± 5.4 and 2.4 ± 1.0 ng/mL, respectively. The linear regression model with serum Lyso-Gb3 as the dependent variable and DBS Lyso-Gb3 an independent variable was described by the function $y = -1.83 + 1.68 * x$ and showed a high coefficient of determination, $R2 = 0.976$. The overall correlation between the Lyso-Gb3 levels in DBS and sera was high ($R = 0.99$; p b 0.001). Conclusion: DBS provides a convenient, sensitive, and reproducible source to measure Lyso-Gb3 levels for diagnosis, initial phenotypic assignment, and therapeutic monitoring in patients with Fabry disease.

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Supplementary Table A1. Dry Blood Spot and Serum LysoGb3 Concentrations in Affected Males and Heterozygotes with the Classic and Later-Onset Phenotypes of Fabry Disease.

A. Classic Males

Age	GLA Mutation	Predicted Enzyme Protein Change	DBS Lyso-Gb3 level (ng/ml)	Serum Lyso-Gb3 level (ng/ml)
27	c.559_560delAT	p.M187Vfs*6	89	148
29	c.1147_1149del	p.F383del	70	118
49	c.744_745delTA	p.F248LfsX7	37	65
46	c.744_745delTA	p.F248LfsX8	60	92
50	Deletion exon 2		72	130
31	c.1055_1057dupCTA	p.A352_M353insT	36	45
44	c.581C>T	p.T194I	28	33
67	c.581C>T	p.T194I	28	35
51	c.581C>T	p.T194I	22	32
47	c.613C>T	p.P205S	12	17
55	c.899T>A	p.L300H	47	83
39	c.827G>A	p.S276N	27	46
35	c.125T>C	p.M42T	22	37
63	c.1033T>C	p.S345P	29	52
39	c.1033T>C	p.S345P	13	26
30	c.679C>T	p.R220X	41	58
44	c.370-2A>G	Cons. Splice Site	28	58
35	IVS3+58C>G	p.Y184Nfs*26	22	28

B. Classic Heterozygotes

Age	GLA Mutation	Predicted Enzyme Protein Change	DBS Lyso-Gb3 level (ng/ml)	Serum Lyso-Gb3 level (ng/ml)
62	c.744_745delTA	p.F248LfsX7	6.6	8.6
41	c.744_745delTA	p.F248LfsX7	2.9	3.9
23	c.744_745delTA	p.F248LfsX7	5.2	7.9
27	c.1147_1149del	p.F383del	6.8	7.2

50	c.365delA	p.N122IfsX8	17	20
38	c.1235_1236delCT	p.N122IfsX8	4.6	6.3
33	c.1055_1057dupCTA	p.A352_M353insT	7.3	7.4
37	c.1167dupT	p.V390CfsX9	13	24
53	c.1167dupT	p.V390CfsX9	6.8	9.9
26	c.1167dupT	p.V390CfsX9	5.6	7.6
70	c.1033T>C	p.S345P	8.3	8.6
42	c.1033T>C	p.S345P	6.7	7.8
30	c.1033T>C	p.S345P	8.7	13
34	c.581C>T	p.T194I	6.0	6.1
63	c.581C>T	p.T194I	4.7	8.2
37	c.581C>T	p.T194I	6.2	5.6
70	c.581C>T	p.T194I	13	27
34	c.581C>T	p.T194I	9.7	8.3
39	c.581C>T	p.T194I	5.2	8.7
67	c.581C>T	p.T194I	9.5	13
48	c.72G>A	p.Y24X	7.0	14
63	c.72G>A	p.Y24X	7.4	9.3
35	c.901C>T	p.R301X	8.9	9.7
50	c.870G>C	p.M290I	1.3	0.37
26	c.125T>C	p.M42T	4.5	6.9
58	c.796G>T	p.D266T	5.3	8.2
41	c.640-3C>G	Cons. Splice Site	5.6	11
67	c.370-2A>G	Cons. Splice Site	8.2	14
55	c.796G>T	p.D266T	8.2	12
65	IVS3+58C>G	p.Y184Nfs*26	5.1	7.5

C. Later-Onset Males

Age	GLA Mutation	Predicted Enzyme Protein Change	DBS Lyso-Gb3 level (ng/ml)	Serum Lyso-Gb3 level (ng/ml)
39	c.902G>A	p.R301Q	23	34
65	c.902G>A	p.R301Q	6.3	10

46	c.902G>A	p.R301Q	4.1	6.1
41	c.337T>C	p.F113L	5.4	15
63	c.644A>G	p.N215S	3.1	5.3

D. Later-Onset Heterozygotes

Age	GLA Mutation	Predicted Enzyme Protein Change	DBS Lyso-Gb3 level (ng/ml)	Serum Lyso-Gb3 level (ng/ml)
75	c.902G>A	p.R301Q	2.6	3.6
33	c.337T>C	p.F113L	1.3	1.6
43	IVS4+919G>A	Alt. Splice Mut.	1.1	2.1